REMARKS

At the outset, Applicant wishes to thank the Examiner for withdrawal of the rejection under 35 U.S.C. 112 first paragraph. In response to the Final Office Action mailed October 21, 2010, and having a period for response set to expire on January 21, 2011, Applicant respectfully requests that the Examiner favorably consider the following remarks.

Status to the claims

With the present submission, no claims are amended. Claims 1-17 and 21-32 were previously canceled without prejudice. Thus, claims 18-20 and 33-49 are presently under consideration.

Claim Rejections – 35 U.S.C. 103(a)

The Office rejected claims 18-20 and 33-49 under 35 U.S.C. 103(a) as allegedly being obvious over Elbashir (EMBO J., 2001, 20(23):6877) in view of Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, 6:1077-87), and Crooke (US 5,898,031). Applicant respectfully traverses the rejection.

Applicant maintains the arguments presented in the response filed on August 16, 2010. In response to the Examiner's "Response to Arguments" provided in the Final Office action mailed on October 21, 2010, Applicant respectfully traverses and wishes to comment briefly on what appears to be a simple mischaracterization of the prior art. Specifically, the Office asserts that "the instant claims require a total of 10 pyrimidines of the sense and antisense strand to be modified (deminimus of the claim), which can be concentrated in the terminal regions which is consistent with the teachings of Elbashir et al., wherein the board agreed that Elbashir et al. is silent as to the data between 19% modification of the duplex and 100% modification of one or both strands" (Final Office Action, pages 10-11). However, Applicant, in reading both the Elbashir et al. reference and the decision of the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), respectfully cannot find support for either the assertion that (1) Elbashir teaches modification of the terminal regions of the siRNA duplex and (2) that

the board agreed that Elbashir et al. is silent as to the data between 19% modification of the duplex and 100% modification of one or both strands.

Elbashir et al. does not teach modification of the terminal regions of a siRNA duplex, i.e., both 3' and 5' ends of one or both strands. There is simply no teaching or suggestion provided by Elbashir of any successful modification beyond the 2-4 nucleotides at the 3'-terminus of each strand only. Here, the instant claims require terminal caps at the 3' and 5' ends of the sense strand, and the 3'-end of the antisense strand. In addition, the instant claims require 10 or more pyrimidine nucleotides of the sense and/or antisense strand to be modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. It is difficult to imagine how the instantly claimed requirements would be concentrated only at the 3'-terminal regions as taught by Elbashir et al. when the instant claims require modification of both 3' and 5'-ends of the sense strand, in addition to modification of the 3'-end of the antisense strand, in addition to modification of 10 or more pyrimidine nucleotides of the sense and/or antisense strand. The instant claims require significantly more extensive modification beyond what Elbashir et al. predicted would still allow for RNAi activity based on their understanding of the RNAi mechanism at the time of the invention.

In fact, the teachings of the Elbashir reference have been reviewed by the BPAI who found that "[a] fair reading of [Elbashir]...is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi." Appeal 2009-002562, at page 27. This fair reading is consistent with the position that extensive modification and, in particular, modification beyond the 3'-terminal regions of one or both strands of a siRNA molecule, is either expressly taught away from, or in the alternative, is highly unpredictable in view of the teachings of Elbashir et al., especially since their conclusions were premised on mechanistic incompatability, i.e., that more extensive modifications interfere with protein association for siRNP assembly.

Citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314 (Fed. Cir. 2009), the Office recognized in the Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex (Notices) that,"[a]n inference that a claimed

combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." Fed. Reg. 75:169 (September 1, 2010) page 53649. Clearly, one of skill in the art, having read the teachings of Elbashir et al., who warn against more extensive modification beyond the 3'-terminal regions due to proposed mechanistic concerns over the ability of the siRNA to associate with proteins required for RNAi would certainly not have any reasonable expectation of success in arriving at active molecules as claimed. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing, Applicant respectfully submits the pending claims are in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,

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